REMARKS

Claim Status

Claims 6, 7, 13, 16-41, 47 and 48 are cancelled.

Claims 44-46 are withdrawn.

Claim 3 is currently amended.

Applicants respectfully submit that the foregoing amendment to the claims does not introduce any new subject matter to the application. With the present amendment, there are eighteen claims pending, namely claims 1-5, 8-12, 14, 15, 42-46 and 49.

Claim Rejections – 35 USC § 112, first paragraph (Written Description)

Claims 1-3, 8-12, 14, 15, 42, 43 and 49 stand rejected under 35 USC § 112, first paragraph, as lacking written description by the specification. In lodging this rejection, the Examiner draws attention to claim 3:

> [A]n *E. coli* glutamate dehydrogenase having a leucine at the amino acid position that corresponds with amino acid 92 of a wild type glutamate dehydrogenase is not limited to only the substitution at position 92 since the transitional phrase 'having' does not create a presumption that the body of the claim is closed...Therefore, while the variant glutamate dehydrogenase comprises the recited substitution, the same variant glutamate dehydrogenase can comprise any amino acids in any other positions.

Office Action, page 3 (line 20) – page 4 (line 3). On this basis, the Examiner contends that the non-standard amino acid degrading proteins (NSAADPs) recited by the claims have "unknown structure."

Applicants respectfully disagree with these allegations. However, claim 3 as currently amended does not recite the open-ended transitional term "having." Applicants further take this opportunity to emphasize that the NSAADP genus recited in the claims is specific to glutamate dehydrogenases, leucine dehydrogenases, valine dehydrogenases, phenylalanine dehydrogenases and glutamate/leucine/phenylalanine/valine dehydrogenases. As presented in the February 17,

2009 Response, not only are multiple examples of these NSAADPs disclosed in the specification by way of reference, but these type of enzymes are well known in the art. This disclosure and level of knowledge in the art are further contrary to the allegation that the recited NSAADPs have "unknown structure." Again, Applicants are not required, and even urged against, describing invention features that are "well-known to those skilled and already available to the public" (MPEP § 2164.05[a]). In view of the above amendment and remarks, Applicants respectfully submit that this rejection is overcome.

Claim Rejections – 35 USC § 112, first paragraph (Enablement)

Claims 1-3, 8-12, 14, 15, 42, 43 and 49 stand rejected under 35 USC § 112, first paragraph, as not being enabled by the specification. In lodging this rejection, the Examiner draws attention to claim 3:

> [A]n *E. coli* glutamate dehydrogenase having a leucine at the amino acid position that corresponds with amino acid 92 of a wild type glutamate dehydrogenase is not limited to only the substitution at position 92 since the transitional phrase 'having' does not create a presumption that the body of the claim is closed...Therefore, while the variant glutamate dehydrogenase comprises the recited substitution, the same variant glutamate dehydrogenase can comprise any amino acids in any other positions.

Office Action, page 11 (lines 2-8). On this basis, the Examiner contends that the NSAADPs recited by the claims have "unknown structure."

Applicants respectfully disagree with these allegations. However, claim 3 as currently amended does not recite the open-ended transitional term "having." As discussed in the above remarks, the NSAADPs recited in the claims are well known in the art and, therefore, do not have "unknown structure." Hence, those of ordinary skill in the art are more than adequately equipped to practice the claimed method without an undue amount of experimentation. In view of the above amendment and remarks, Applicants respectfully submit that this rejection is overcome.

Claim Rejections – 35 USC § 103(a)

Two different obviousness rejections under 35 USC § 103(a) are lodged in the pending Office Action.

Claims 1, 2, 8-11, 14, 15, 42, 43, 49

In the first rejection, claims 1, 2, 8-11, 14, 15, 42, 43 and 49 are alleged to be obvious over the combination of Wang et al. (2001, *Eur. J. Biochem.* 268:5791-5799), Bogosian et al. (U.S. Patent No. 5,932,439) and Fenton et al. (U.S. Patent No. 5,599,690).

Wang is cited as allegedly disclosing glutamate dehydrogenases (GDH) having increased activity for degrading norleucine. Fenton is cited to establish that the field already knew that non-standard amino acid incorporation in heterologously expressed proteins is problematic, thus allegedly providing a motive for skilled artisans to use the GDHs taught by Wang in deriving the currently claimed invention. Bogosian is cited simply to establish that heterologous protein (e.g., somatotropin) expression was a previously known practice.

In the February 17, 2009 Response, Applicants explained that there would have been no motivation for skilled artisans to derive the claimed invention in view of Wang since GDH degrades methionine and, therefore, would have been expected to negatively affect heterologous protein expression. The Examiner responds by alleging:

> Table 2 on page 5795 discloses that at some pH levels, activity towards Nle is much greater that Met. For example, at pH 8.0, the triple mutant KSA/LAG has no activity towards glutamate, negligible activities towards Leu and Ile, and three times the rate of degrading Nle than Met.

Office Action, page 18 (line 20) – page 19 (line 1). In view of this higher activity of KSA/LAG GDH (pH 8.0) against norleucine compared to methionine, the Examiner alleges that a skilled artisan would have been motivated to use this form of GDH to practice the invention.

Applicants respectfully disagree. While the KSA/LAG GDH (pH 8.0) of Wang is more active against norleucine than methionine, this does not take away the fact that this GDH has appreciable activity against methionine (Table 2). Furthermore, the other GDHs disclosed by Wang to have appreciable activity against norleucine likewise have appreciable activity against methionine (e.g., A163G, K89L/A163G, Table 1 and 2). These additional data would have further reduced motivation for skilled artisans to practice the claimed invention with Wang's GDHs.

In the February 17, 2009 Response, Applicants further made two separate arguments: (i) that it would have been unpredictable to use the GDHs taught by Wang to derive the claimed invention, and (ii) that the results obtained with the claimed invention are unexpected. However, the Examiner assesses these arguments as being interrelated:

> Applicants also argue that the motivation to use wild type and mutant forms of Wang et al. [GDHs] is further eroded by unpredictability inherent to extending *in vitro* enzymatic observations to *in vivo* conditions since the claimed invention provided unexpected results...Obviousness does not require absolute predictability.

Office Action, page 19 (lines 10-18). Applicants respectfully indicate that their arguments of unpredictability and unexpected results were not hinged together, and therefore kindly reiterate their remarks from the February 17, 2009 Response concerning unexpected results. When applying the claimed method as described in Example 2 of the specification, Applicants were able to produce recombinant somatotropin for amino acid content analysis. Such expression of a heterologous protein is surprising in view of the negative effects on protein translation that would have been expected to occur in attempting to overexpress NSAADPs such as those taught by Wang. Therefore, while the claimed invention is non-obvious for motivation purposes (above remarks), it is also non-obvious given unexpected results, which are an indicator of non-obviousness (MPEP § 716.02).

Claims 3-5, 12

In the second rejection, claims 3-5 and 12 are alleged to be obvious over the combination of Wang, Bogosian and Fenton, in further view of Rice et al. (1996, *FEMS Microbiol. Rev.* 18:105-117). The Examiner alleges that Wang discloses a mutant GDH that has increased activity for degrading norleucine; this GDH carries a K89L amino acid change and is derived from *Clostridium symbiosum*. As disclosed by Rice, *C. symbiosum* K89L GDH is allegedly of similar structure to *E. coli* K92L GDH, where position 89 in the former enzyme corresponds to position 92 in the latter enzyme (Rice also alleges that the wildtype forms of these enzymes are structurally similar).

First and foremost, Applicants respectfully contend that claims 3-5 and 12 are non-obvious, given that base claims 1 and 2 are non-obvious over Wang, Bogosian and Fenton (refer to above remarks). However, claims 3-5 and 12 are non-obvious for additional reasons.

In the February 17, 2009 Response (page 14), Applicants argued that the invention as recited in claims 3-5 and 12 was non-obvious given unexpected results obtained comparing wildtype and K92L forms of *E. coli* GDH. Briefly, Applicants submitted that it was surprising that wildtype *E. coli* GDH had norleucine-degrading activity – almost the same as the activity of K92L *E. coli* GDH – in view of Wang's teaching that the structurally similar wildtype GDH counterpart from *C. symbiosum* **lacks** such activity (e.g., Tables 1 and 4). The Examiner considers this argument as "moot" since the rejection was "not based on using wildtype E. coli GDH, but a mutant E. coli [GDH] comprising a mutation at a position corresponding to position 89 of the wildtype *C. symbiosum* [GDH] of Wang et al." (Office Action, page 20, lines 6-9).

In response, Applicants respectfully submit that it is also important to consider the corollary of the above observation, that the activity of K92L GDH was not greatly increased over the activity of wildtype GDH. Wildtype and K92L GDHs decreased the percentage of

norleucine in a heterologously expressed protein to 0.9% and 0.6%, respectively (from 17.4% in control) (specification, Table 5, rows 1-3). Based on Wang's teaching that *C. symbiosum* K89L GDH has norleucine-degrading activity (e.g., Tables 2 and 4) and that wildtype *C. symbiosum* GDH does not have this activity (e.g., Tables 1 and 4), skilled artisans would have expected *E. coli* K92L GDH to have substantially greater norleucine-degrading activity compared to wildtype *E. coli* GDH. This deficiency constitutes an absence of an expected property, thereby further speaking to the non-obviousness of the claimed invention ("Absence of [a] property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness," MPEP 716.02[a][IV]).

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Applicants do not believe that any fee is due in relation to filing this document. However, the Commissioner is hereby authorized to charge any underpayment of fees to Howrey LLP Deposit Account 08-3038/11916.0059.PCUS01.

Respectfully submitted,

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